IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo et al.

SERIAL NO.: 09/770,562

FILED: January 26, 2001

FOR: Solid Pharmaceutical Dispersions With Enhanced Bioavailability

Examiner: B. Fubara
Art Unit: 1618

Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Dwayne T. Friesen, declare that:

1. I was awarded the degree of Bachelor of Science in Chemistry in 1975 by California State College at Bakersfield, and subsequently was awarded a Ph.D. in Physical Chemistry in 1980 at Oregon State University. I have been employed by Bend Research, Inc., of which I am also part owner, up to the present time. My current title is Vice President, Research. I am a member of the Board of Directors of Bend Research, Inc.

2. Bend Research, Inc., is part-owned by Pfizer, Inc., the Assignee of the above-identified U.S. application.

3. As part of an ongoing investigation into the properties of spray dried dispersions, experiments were conducted measuring the Maximum Supersaturated Concentration of dissolved drug (MSSC) achieved during the

initial 90 minutes (the physiologically relevant time period) in an *in vitro* dissolution media by spray dried dispersions of amorphous drugs dispersed in hydroxypropylmethyl cellulose acetate succinate (HPMCAS). Attached as Exhibit A is a summary of the experiments conducted for 10 different drugs. Four of these drugs were described in the examples in the patent application (Drugs 1, 2, 3 and 9) and six additional drugs were also tested (Drugs A-F).

4. Several of the drugs were neutral (non-ionizable) e.g., (Drugs, 1, 9, A, B, and D) and several were at least partially ionizable, Drug E being acidic, Drug C being weakly acidic, and Drugs 2, 3, and F being basic.

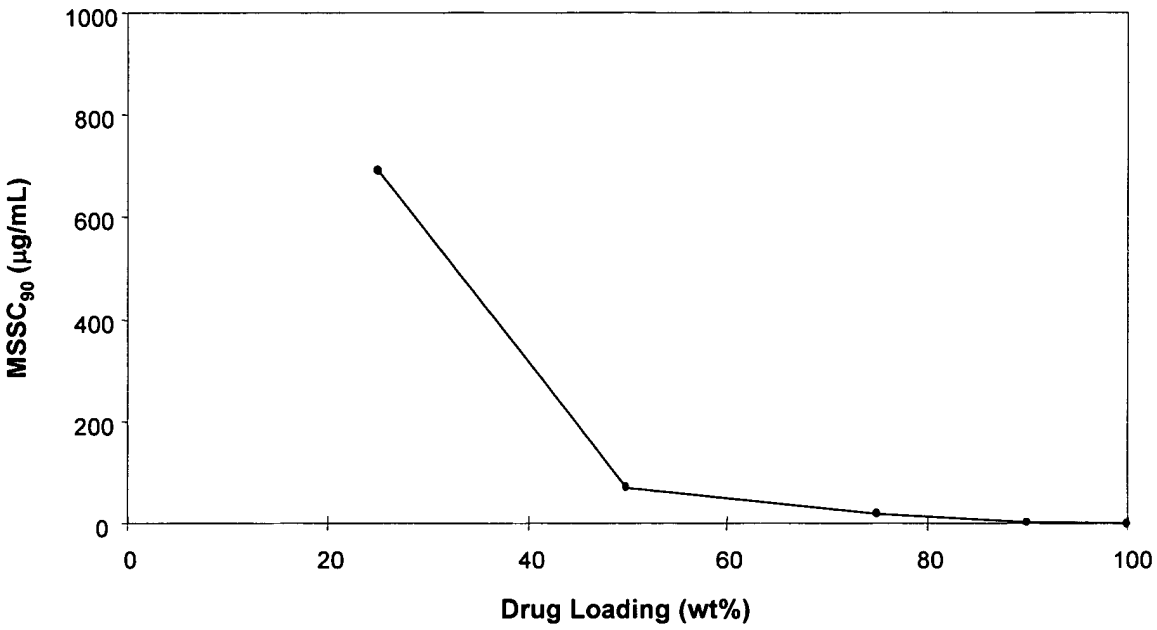
5. As part of these experiments, the drug nicardipine was tested (Drug F). Nicardipine was selected because, as between nicardipine and nifedipine, nicardipine has the closest chemical structure to the drug NZ-105 reported in Miyajima, et al., US Patent No. 4,983,593, in that it has similar functional groups (tertiary amine and a substituted cyclic amine) as well as similar physical properties (solubility, logP, and melting point). (NZ-105 could not be obtained to perform the experiments.)

6. For all of the drugs tested, the same general trend was observed showing that the MSSC achieved for the drug varied inversely in proportion to the amount of drug in the solid amorphous dispersion. That is, as the amount of drug in the solid amorphous dispersion increased, the MSSC decreased. This was true for acidic drugs, basic drugs, and neutral drugs.

7. In particular, dispersions containing the drug torcetrapib (Drug A) were further analyzed to determine the relationship of the amount of drug in the solid amorphous dispersion, MSSC, and the homogeneity of the dispersion.

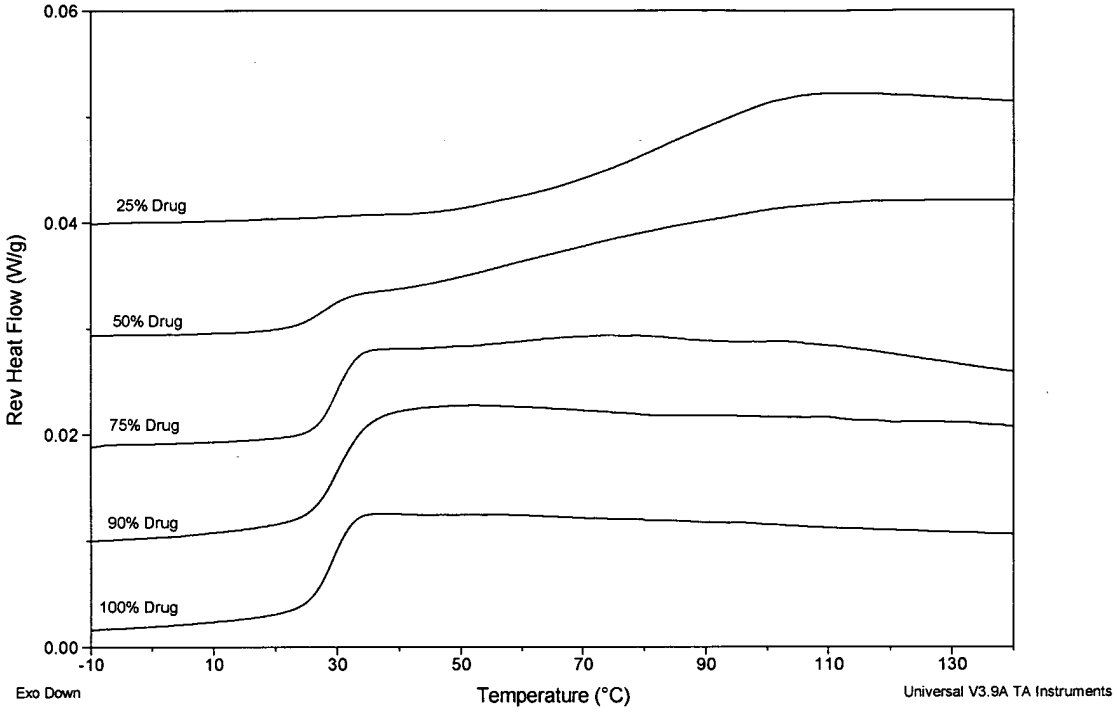
8. Figure 5 of Ex. A (reproduced below) is a graph that plots the MSSC achieved for the drug torcetrapib (Drug A) in phosphate buffered saline solution at different ratios of drug to polymer.

Figure 5. $MSSC_{90}$ Versus Drug A Loading



9. In addition, spray dried solid amorphous dispersions of torcetrapib and HPMCAS of the type used for the results in Figure 5 above were analyzed using Differential Scanning Calorimetry (DSC) to determine the degree of homogeneity of the dispersions. Samples were equilibrated in open pans for a minimum of 18 hours at relative humidity (RH) controlled at less than 5%. Sample pans were non-hermetically sealed in an environmental chamber, then loaded into the furnace of a TA Instruments Q1000 DSC with a robotic arm. The samples were cooled to -25°C and then heated to 150°C at 2.5 °C/min., while modulating the temperature at $\pm$ 1.5°C every 60 seconds. The results are shown below in Figure 11.

Figure 11. DSC Analysis of Dispersions with 25-100% Drug A Loadings



10. The DSC scans in Figure 11 show that the solid amorphous dispersion with 25% drug loading (drug:polymer weight ratio of 1:3) was homogeneous while for solid amorphous dispersions with 50% drug or more, the solid amorphous dispersions had a distinct drug phase. In addition, as drug loading increased above 50 wt%, the degree of phase separation increased. From the DSC scans, a separate glass transition temperature (T_g) at about 30°C is observed for solid amorphous dispersions having a drug loading of at least 50%. The glass transition temperature at about 30°C corresponds to the T_g of amorphous drug alone (no polymer), which is confirmed by the bottom DSC trace of drug alone with no polymer. This thermal event at the pure drug glass transition temperature increases in intensity as the drug loading increases above 50%. For the solid amorphous dispersion with 25% drug loading (top line) no separate glass transition temperature corresponding to the drug alone is observed at 30°C, and only a single glass transition temperature is observed

corresponding to the T_g of the homogeneous solid amorphous dispersion (about 80-90°C). For the solid amorphous dispersion with 50% drug loading, a small glass transition temperature is observed at lower temperature (at about 30°C), as well as a second glass transition temperature at about 80-90°C. This indicates some of the drug is in a separate phase, but much of the drug is still dispersed in the polymer. For the 75% drug loading and 90% drug loading materials only one glass transition is observed at a temperature of about 30°C, corresponding to an amorphous drug alone. The intensity of this transition is greater than that of the solid amorphous dispersion with 50% drug loading.

11. As shown in Figure 11, the homogeneity of the solid amorphous dispersions increases as the drug loading (wt%), or drug to polymer ratio, decreases.

12. As can be seen by comparing the results of Figure 5 with the results of Figure 11, homogenous dispersions achieve better dissolution performance than dispersions which are not homogenous.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the likes made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Jan. 17, 2006
Date

Dwayne T. Friesen

G:\BRI Corporate\Legal\Patent\PC 9674 HPMCAS SDDs\Dwayne Friesen Declaration for interview A-F.doc

Exhibit A

HPMCAS Dispersions of Drugs with Varying Drug Loadings

I. Drugs from Patent Examples

Spray dried solid amorphous dispersions of Drugs 1, 2, 3, and 9 from the patent application were made with HPMCAS (M or H grade) at various drug loadings. The dispersions were dissolution tested to evaluate concentration-enhancement of the drugs *in vitro*. For each test, a sufficient amount of material was added to microcentrifuge tubes in duplicate such that the reported theoretical Maximum Supersaturated Concentration (MSSC) would have been achieved, if all of the drug had dissolved. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL PBS (pH 6.5 and 290 mOsm/kg), or PBS with 0.5 wt% NaTC/POPC (MFDS), was added to each respective tube. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:6 (by volume) with methanol and then analyzed by high-performance liquid chromatography (HPLC). The contents of each respective tube were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 4, 10, 20, 40, 90, and 1200 minutes. Table 1 shows the dispersions tested, theoretical MSSC, and dissolution media used.

Table 1

Dispersion	Drug Loading (wt%)	Theoretical MSSC (μg/mL)	Media
Drug 1: HPMCAS-M	10	500	MFDS
	11.1		
	12.5		
	14.3		
	16.7		
	33		
	67		
	100		
Drug 2: HPMCAS-M	10	100	MFDS
	17		
	33		
Drug 3: HPMCAS-H	10	200	MFDS
	25		
	50		
	75		
	90		
Drug 9: HPMCAS-M	10	2000	PBS
	25		
	33		
	50		
	75		
	100		

Figures 1 through 4 graph MSSC within ninety minutes ($MSSC_{90}$) achieved during dissolution testing versus drug loading for the dispersions in Table 1. Solid amorphous dispersions with Drug 1, Drug 2, Drug 3, and Drug 9 all show a decrease in MSSC with increasing drug loading.

Figure 1. $MSSC_{90}$ Versus Drug 1 Drug Loading

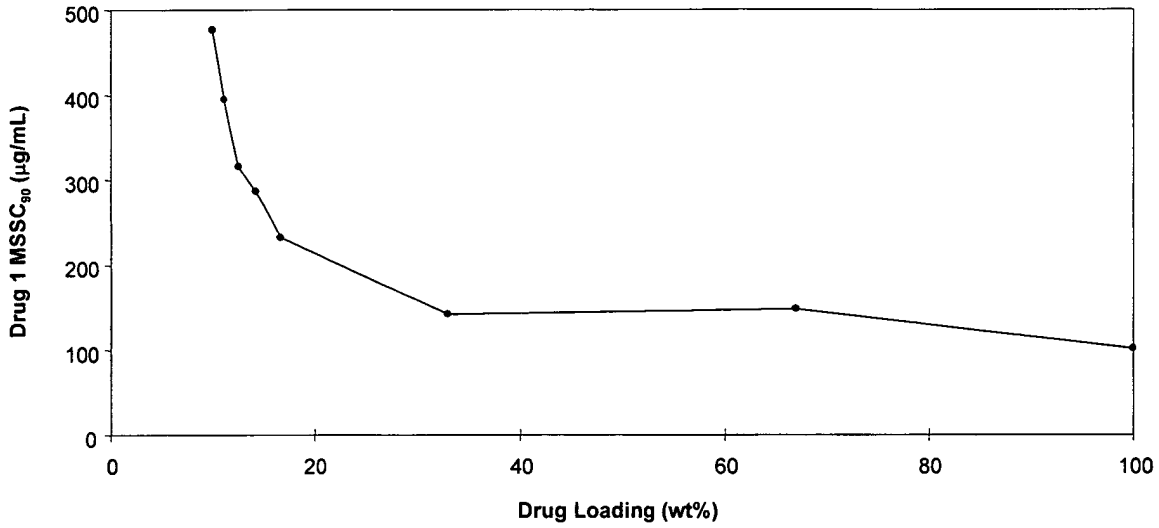


Figure 2. $MSSC_{90}$ Versus Drug 2 Drug Loading

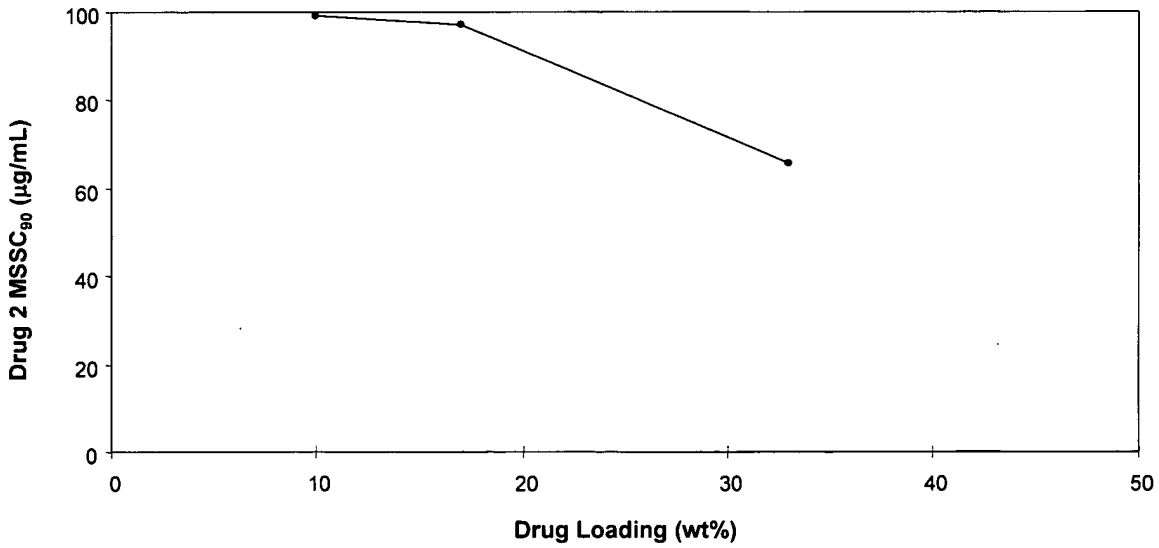


Figure 3. $MSSC_{90}$ Versus Drug 3 Drug Loading

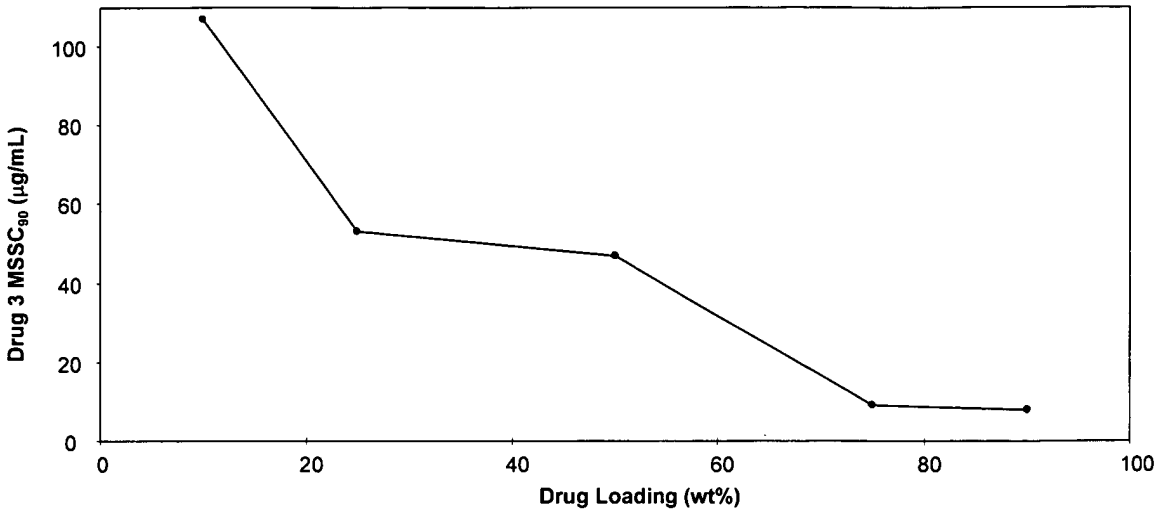


Figure 4. $MSSC_{90}$ Versus Drug 9 Drug Loading

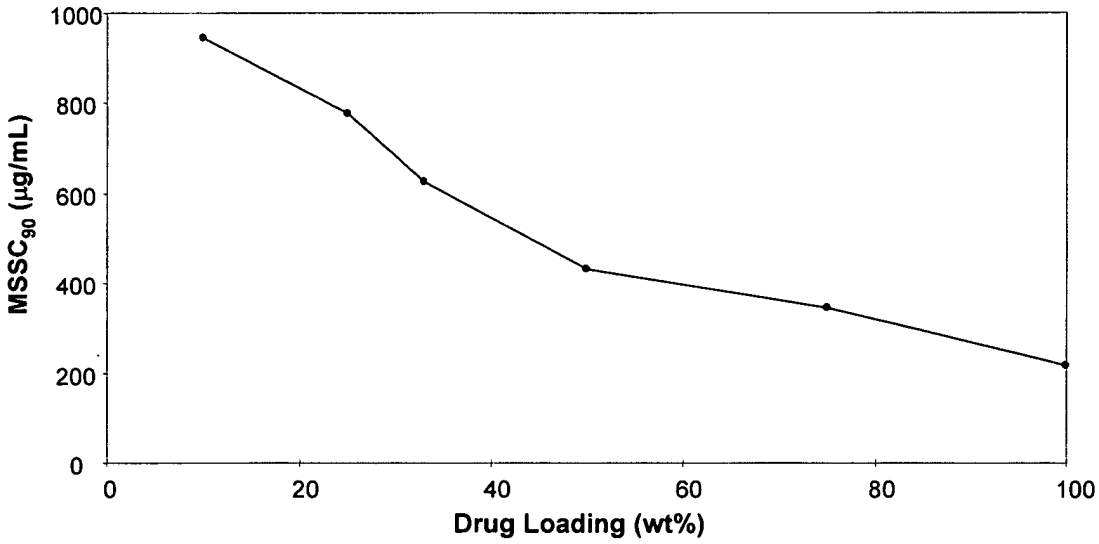
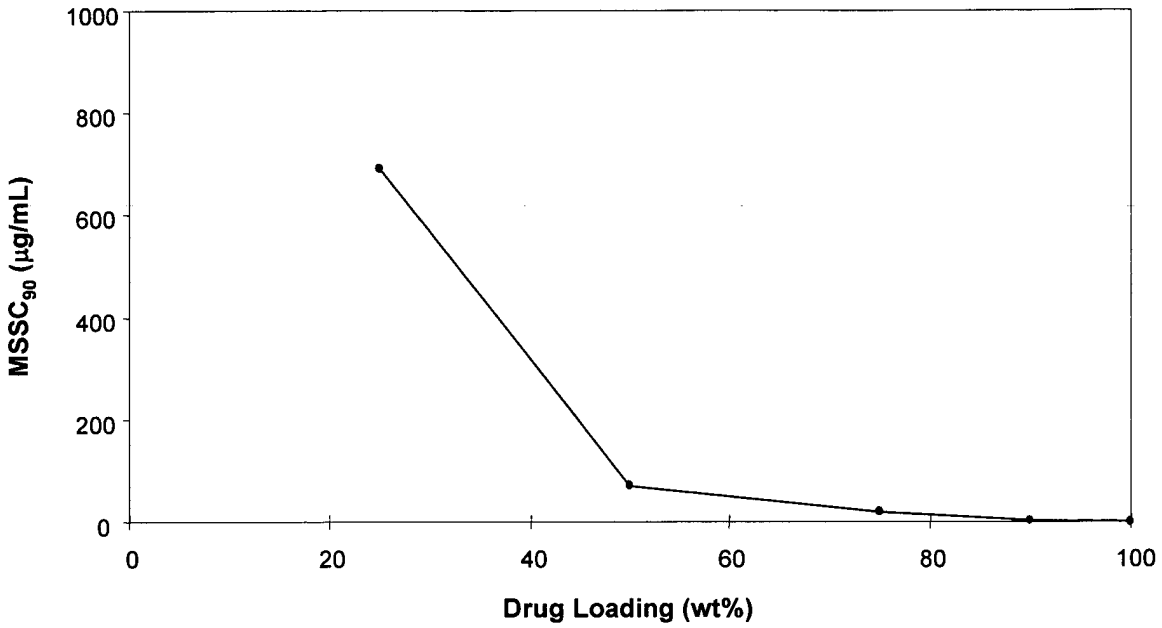
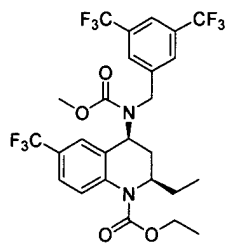


Figure 5. $MSSC_{90}$ Versus Drug A Loading

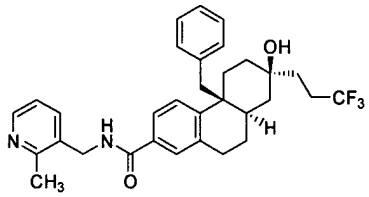


II. Dispersions with Other Drugs

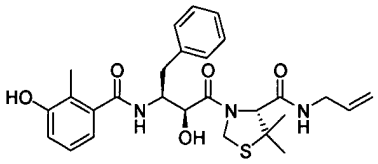
In addition to the drugs in the patent examples, several other drugs were also tested. Spray dried solid amorphous dispersions of Drugs A-F were made with HPMCAS (M or H grade) at various drug loadings as shown in Table 2.



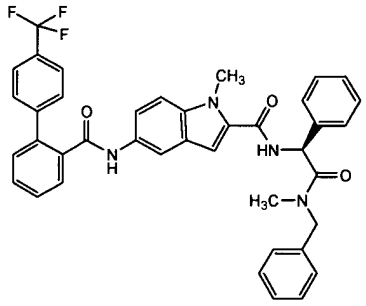
Drug A (Torcetrapib)



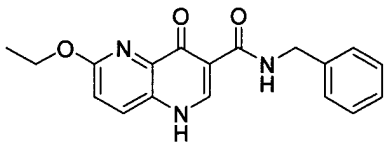
Drug B



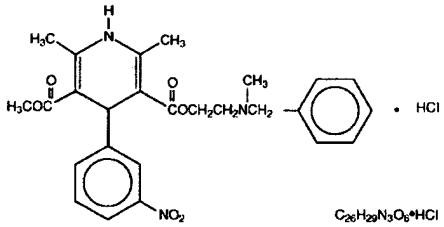
Drug C



Drug D



Drug E



Drug F (nicardipine)

The dissolution properties of the dispersions were tested as described above with the dissolution media shown in Table 2. Dissolution results are shown in Figures 5-11.

Table 2

Dispersion	Drug Loading (wt%)	Theoretical MSSC (μg/mL)	Media
Drug A:HPMCAS-M	25	1000	PBS
	50		
	75		
	90		
Drug B:HPMCAS-M	10	1600	2 wt% NaTC/POPC in PBS
	25		
	50		
Drug C:HPMCAS-M	40	3000	PBS
	50		
	75		
	90		
	95		
	98		
	100		
Drug D:HPMCAS-M	25	500	MFDS
	50		
	95		
Drug E:HPMCAS-H	10	400	MFDS
	25		
	33		
	50		
	75		
	100		
Drug F:HPMCAS-M	25	2000	PBS
	50		
	75		
	90		
	100		

Figure 5. $MSSC_{90}$ Versus Drug A Drug Loading

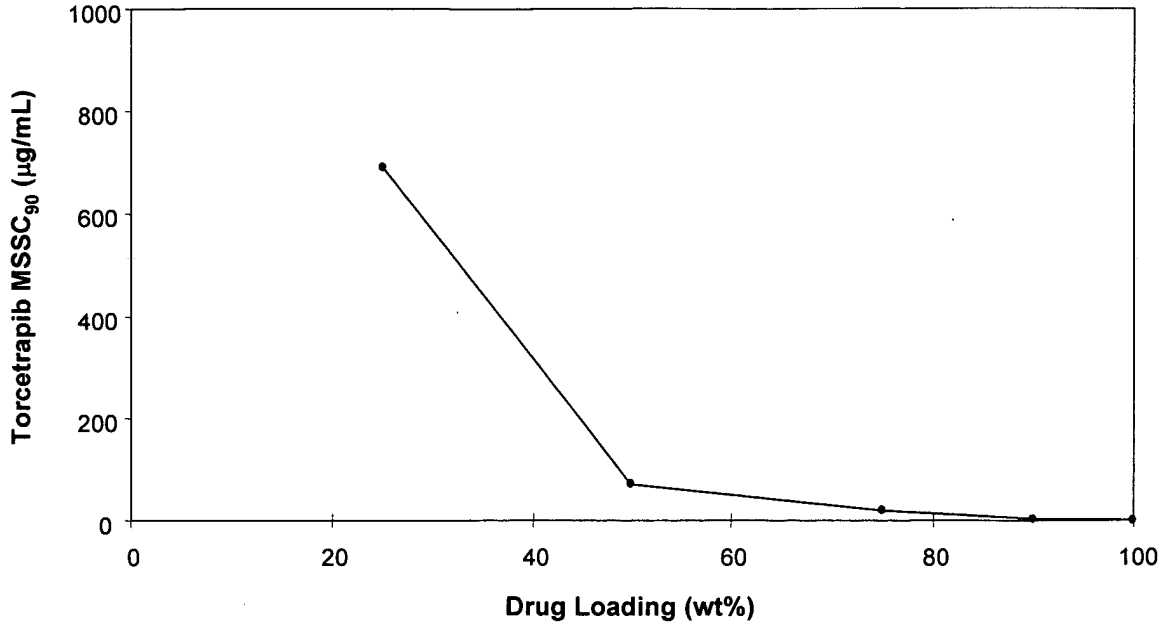


Figure 6. $MSSC_{90}$ Versus Drug B Drug Loading

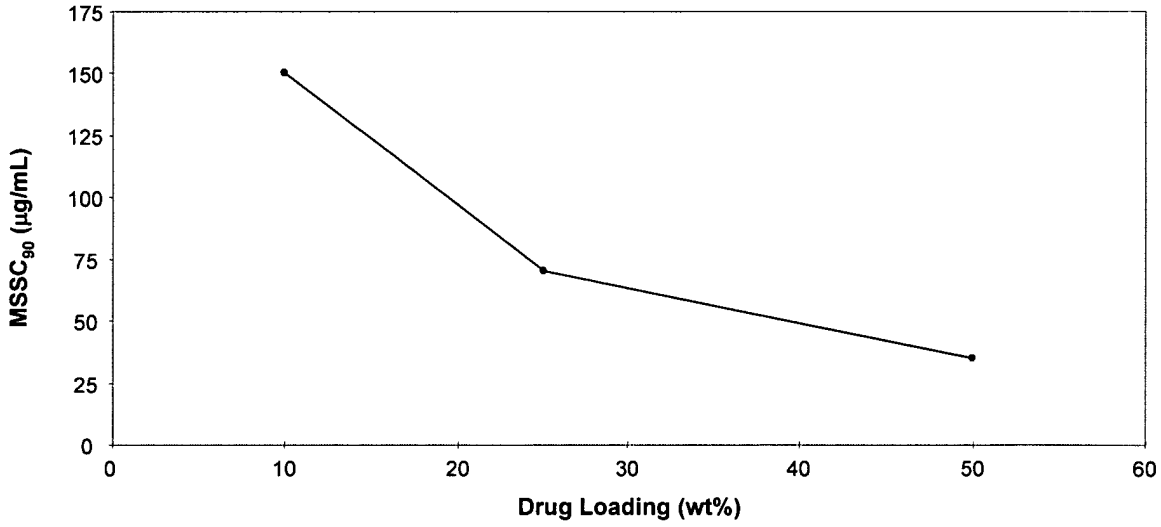


Figure 7. $MSSC_{90}$ Versus Drug C Drug Loading

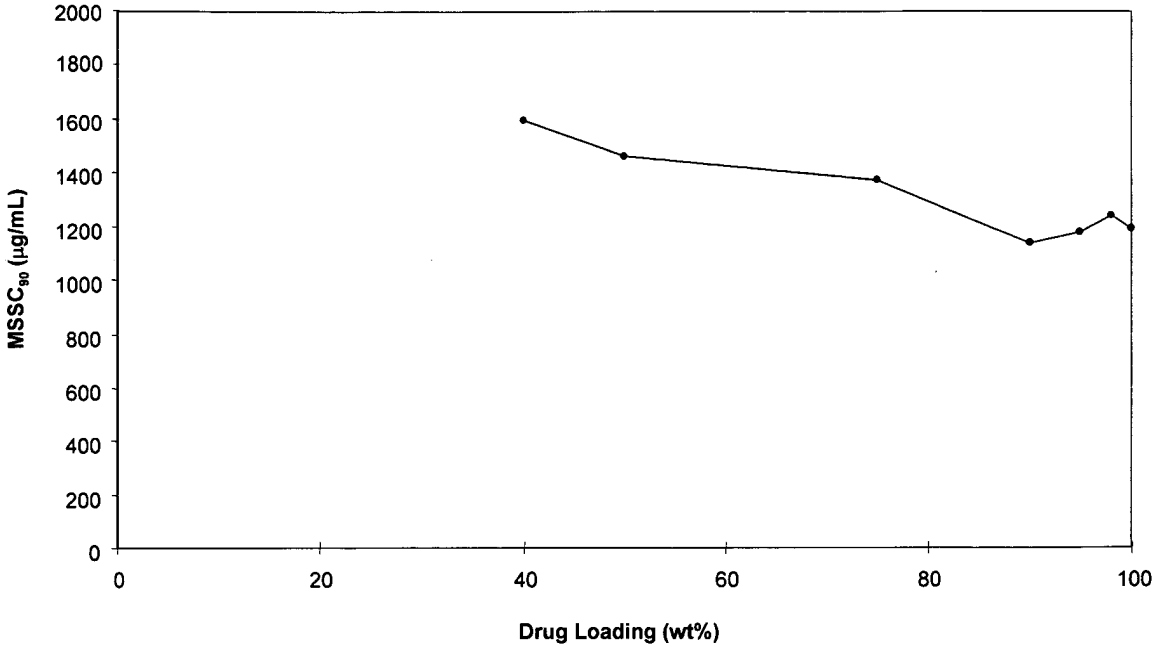


Figure 8. $MSSC_{90}$ Versus Drug D Drug Loading

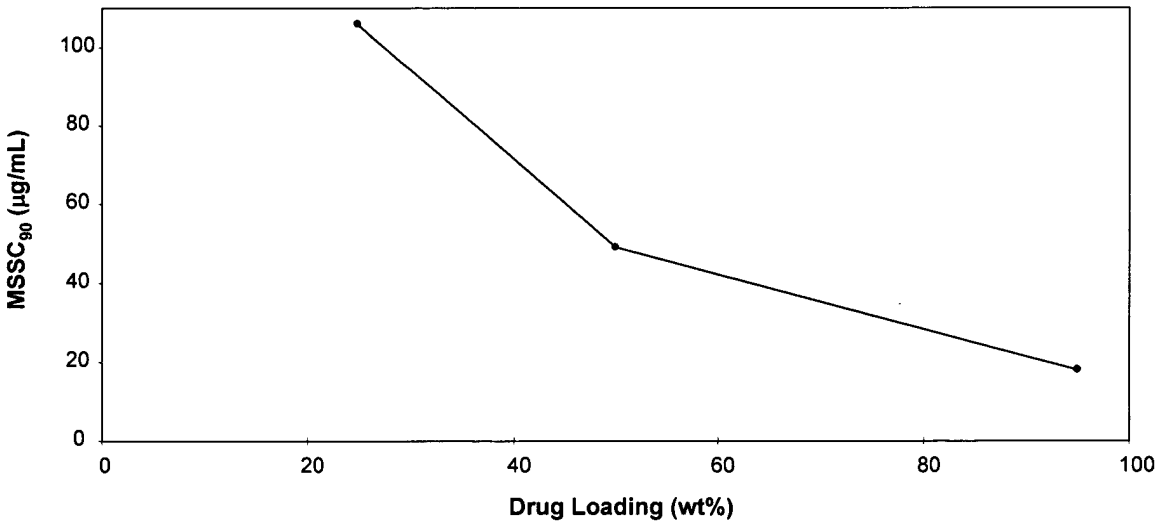


Figure 9. $MSSC_{90}$ versus Drug E Drug Loading

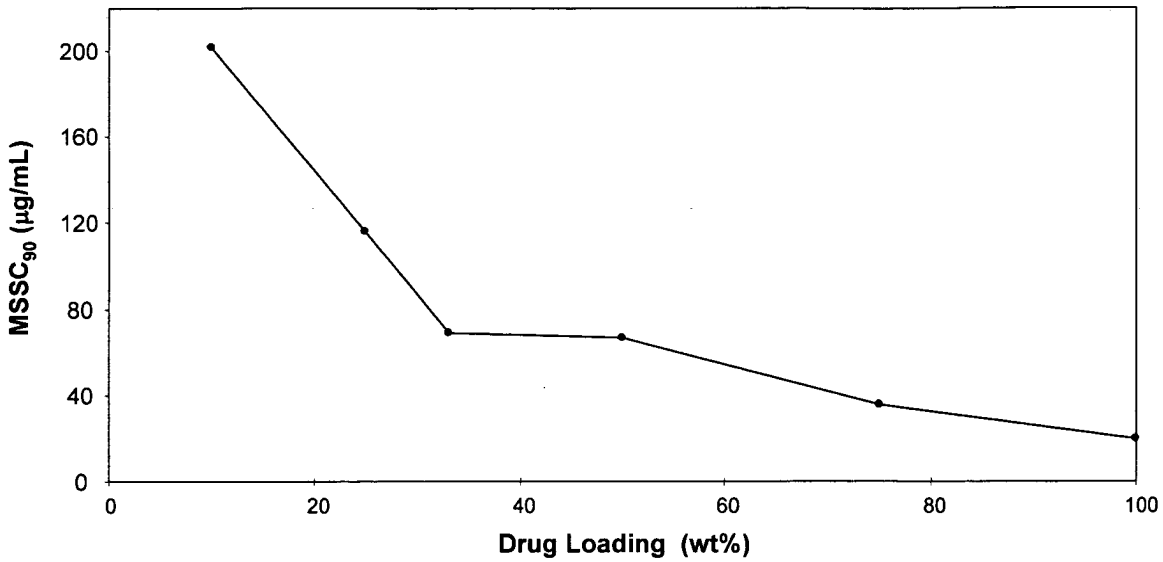


Figure 10. $MSSC_{90}$ Versus Drug F Drug Loading

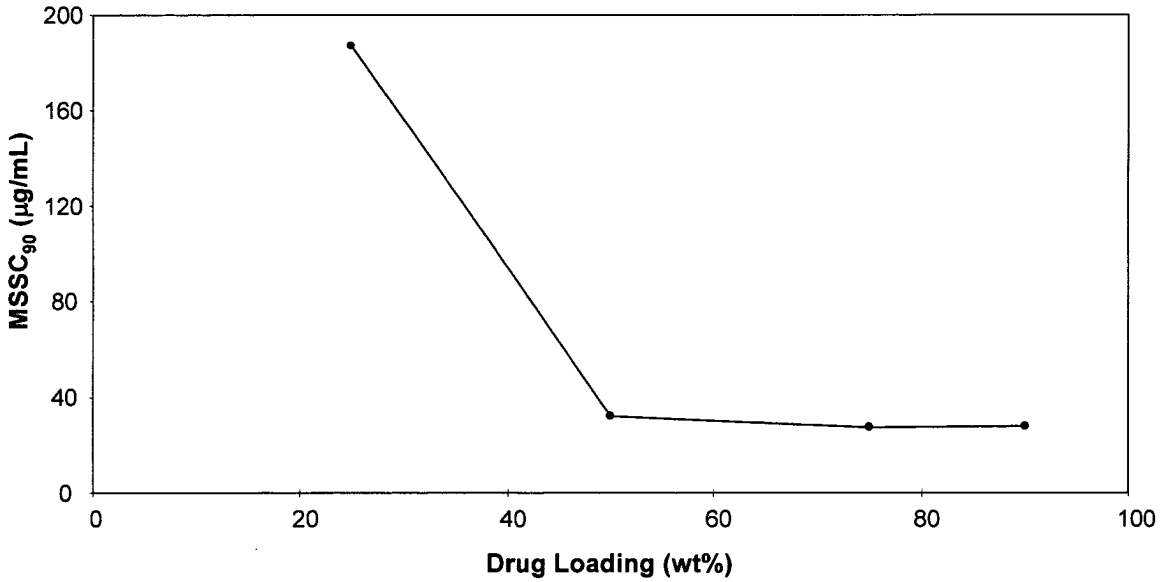


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EXHIBIT A

PATENT PC9674AJTJ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: **William J. Curatolo, et al.**

: Examiner: **W. Benston Jr.**

SERIAL NO.: **09/131,019** : Art Unit: **1615**

FILED: **August 7, 1998** :

FOR: **Solid Pharmaceutical Dispersions With Enhanced Bioavailability**

Assistant Commissioner For Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Dwayne T. Friesen, declare that:

1. I was awarded the degree of Bachelor of Science in Chemistry in 1975 by California State College at Bakersfield, and subsequently was awarded a Ph.D. in Physical Chemistry in 1980 at Oregon State University. I have been employed by Bend Research, Inc., of which I am also part owner, up to the present time. My former title was Director of Research. My current title is Vice President, Research. I am a member of the Board of Directors of Bend Research, Inc.

2. Bend Research, Inc., is part-owned by Pfizer, Inc., the Assignee of the above-identified US application.

3. By virtue of my expertise and work on the project area of pharmaceutical dispersion technology, from which this application originated, I am aware of the application which, as stated above, is owned by Pfizer, Inc., by virtue of an assignment recorded at Reel/Frame 9148/0782. I have read the Final Office Action which was mailed on April 11, 2000 and am aware of the rejection of claims 1 – 38, over US patent 5,456,923 (hereinafter "Nakamichi") as set forth therein.

4. Under my direction, and as described in the Experimental Protocol attached hereto, three Trials were conducted whereby, in each Trial, a spray dried dispersion

(SDD) and a rotary evaporated dispersion (RED) were made for each of three drugs, dissolution tested, and compared. The drugs were, respectively:

Compound 1, the compound disclosed in Applicants' Example 1;
Compound 5, nifedipine, as disclosed in Applicants' Example 28;
Compound 8, the compound disclosed in Applicants' Example 31;

5. The three Trials, including the results therefrom, are reported in detail in the attached Experimental Protocol, which forms a part of this Declaration and is incorporated by reference herein.

6. The object of the three Trials was to compare the dissolution of each of the above three compounds in spray dried dispersions (SDDs) versus rotary evaporated dispersions (REDs); plain crystalline drug added to solution (i.e., no dispersing polymer, spray drying, or rotary evaporation) was used as a control, as appropriate. Each trial is reflective of different conditions, as follows:

Trial 1 - - Used the same dissolution test method as described in Applicants' specification in Example 3, except that the phosphate buffered saline was substituted for model fasted duodenal solution as the dissolution media. The dissolution medium was maintained at 37°C during dissolution testing. Sample work up was by centrifugation at 13,000 G for one minute;

Trial 2 - - Used the test method described in Nakamichi. Nakamichi's method used JP-2 test solution at 25°C as a dissolution medium and 40,000 G as a centrifugation speed for one hour;

Trial 3 - - Used a modified version of the Nakamichi method. The method used Nakamichi's JP-2 test solution, but under the more physiologically relevant conditions of 37°C (i.e., human body temperature), gentler centrifugation conditions – a centrifugation speed of 13,000 G for 1 minute, and data collection during the first three hours of dissolution testing.

7. In each trial, samples of each drug were taken from the individual dissolution media at various time points. For Trials 1 and 3, sample time points were 0, 5, 30, 60, 120, 180 minutes, and 1440 minutes; for Trial 2, sample time points were 0, 60, 120, 180 minutes, and 1440 minutes. 1440 minutes (24 hrs) was included because that is the single time point at which Nakamichi made his dissolution concentration

measurements. The Nakamichi time point is, however, considered physiologically irrelevant since absorption of a drug takes place primarily during the first several (i.e., 1-4) hours following ingestion. Data for the time interval AUC of 0 to 180 minutes, AUC_{180}, is reported in the Experimental Protocol as being physiologically relevant. From the data, Applicants calculated the area under the curve (AUC) for the 0 to 180 minute time interval (AUC_{180}) from the measured drug concentrations, and measured the maximum concentration of dissolved drug during that time period, $Cmax_{180}$.

8. The data for Trial 1 is shown in Table 2 (raw data) and Table 3 (Summary) in the Trial Protocol. The data demonstrates that the Compound 1 and 5 spray dried dispersions (SDDs) showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values at 180 minutes of 12,900 and 28,400, respectively) as compared to the Compound 1 and 5 rotary evaporated dispersions (RED) (AUC values of 3500 and 19,600). Applicants' SDD values for Compounds 1 and 5 were thus 268% and 44% higher, respectively, than the corresponding RED values. The data shows that the Compound 8 SDD and RED were roughly equivalent (AUC values of 57,000 versus 58,100, respectively). The $Cmax_{180}$ value for all three of the SDDs (93, 196, and 440, respectively) were unexpectedly higher than the corresponding $Cmax_{180}$ values for the REDs (24, 129, and 380, respectively).

9. The data for Trial 2 is shown in Table 4 (raw data) and Table 5 (summary) in the Trial Protocol. The data demonstrates that the Compound 1 and 5 spray dried dispersions (SDDs) showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values at 180 minutes of 3400, and 25,200, respectively) than the Compound 1 and 5 rotary evaporated dispersions (RED) (AUC values of 1400 and 10,500). Applicants' SDD values for Compounds 1 and 5 were thus 142% and 140% higher, respectively, than the corresponding RED values. The $Cmax_{180}$ values for the Compound 1 and 5 SDDs (23 and 191, respectively) were also unexpectedly higher than for their RED counterparts (13 and 113, respectively). The data for Compound 8, including the $Cmax_{180}$, was corrupted for both the SDD and the RED. Although the exact reason is not certain, the undersigned believes that the severe conditions of the Nakamichi centrifugation (40,000 G for one hour) may have spun the polymer and polymer-

associated compound (both the SDD and RED) out of solution, effectively preventing any measurements of concentration or Cmax.

10. The data for Trial 3 is shown in Table 6 (raw data) and Table 7 (summary) in the Trial Protocol. This Trial was conducted as a modification of the Nakamichi method and used Nakamichi's dissolution test solvent, but used gentler (centrifuge) sample workup than Nakamichi (13,000 G for 1 minute as opposed to 40,000 G for 1 hour. Data for Trial 3 was obtained in the case of all three test drugs, as opposed to Trial 2. The data demonstrates that all three of the Compounds 1, 5, and 8 SDDs showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values of 5100, 35,600, and 49,300, respectively) than the three Compound 1, 5, and 8 REDs (1600, 17,000, and 36,200, respectively). Applicants' SDD values for Compounds 1, 5, and 8 were thus 218%, 109% and 36% higher, respectively, than the corresponding RED values. The $Cmax_{180}$ value for each of the SDDs (30, 220, and 300, respectively) were unexpectedly higher than the $Cmax_{180}$ values for the REDs (14, 113, and 220, respectively).

11. In summary, Applicants' data demonstrates for the physiologically relevant test interval of 0 to 180 minutes that:

A. Applicants' SDDs generated much higher concentrations of drug in seven out of eight runs occurring over the three trials. The eighth run showed roughly equivalent values of AUC. The ninth run was corrupted and yielded no useful data.

B. Applicants' SDD $Cmax_{180}$ was higher than the corresponding RED Cmax for every run where $Cmax_{180}$ could be measured (8 out of 8 runs).

C. For the one compound in common between Applicants and Nakamichi, i.e., nifedipine (Compound 5), Applicants' SDDs were unexpectedly much better in terms of both AUC and $Cmax_{180}$.

12. The data accordingly demonstrate that Applicants' SDDs are generally unexpectedly much better than the REDs disclosed in Nakamichi.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

10-6-00

Date

Dwayne T. Friesen

Experimental Protocol

Examples 1-3: Preparation of Spray Dried Dispersions

Amorphous solid dispersions of Compound 1, Compound 5 [nifedipine], or Compound 8, with HPMCAS, were made by mixing the compound in solvent together with HPMCAS to form a solution. For Example 1, the solution comprised 0.33 wt% Compound 1, 2.27 wt% HPMCAS-MF, and 97.40 wt% methanol/acetone (86 wt%/14 wt%). For Example 2, the solution comprised 0.51 wt% Compound 5, 2.55 wt% HPMCAS-MF, and 96.94 wt% ethanol/methylene chloride (70 vol% / 30 vol%). For Example 3, the solution comprised 0.42 wt% Compound 8, 0.83 wt% HPMCAS-LG, and 98.75 wt% methanol/acetone (50 wt%/50 wt%). A portion of each solution was pumped into a "mini" spray-dryer apparatus of the type shown in FIGURE 1 of the pending patent via a syringe pump. For Example 1, the solution was pumped at a rate of 70 mL/hr. For Examples 2 and 3, the solution was pumped at a rate of 60 mL/hr. The spray solution was metered using a Cole Parmer 74900 Series rate-controlling syringe pump. The solution was pumped into a Spraying Systems Co. two-fluid nozzle, Model Number SU1A, with nitrogen as the atomizing gas. The nitrogen was pressurized and heated to a temperature of 110°C to 120°C. The solution was sprayed from the top of an 11-centimeter-diameter stainless-steel chamber. The resulting solid amorphous dispersions were collected on Whatman® 1 filter paper, dried under vacuum, and stored in a desiccator.

Table 1 summarizes the solution preparation variables of the spray dried dispersions (SDD).

Table 1. Preparation Of Spray Dried Dispersions (SDDs)

Ex. No.	Cmpd Mass (g)	Cmpd No.	Polymer Mass (g)	Polymer	Solvent Mass (g)	Solvent
Ex1	3.50	1	24.51	HPMCAS-MF	1050	86 wt% methanol/ 14 wt% acetone
Ex2	2.51	5	12.50	HPMCAS-MF	475	70 vol% ethanol/ 30 vol% methylene chloride
Ex3	0.51	8	1.01	HPMCAS-LG	120	50 wt% methanol/ 50 wt% acetone

Comparative Examples 1-3: Preparation of Rotary Evaporated Dispersions

A portion of each of the solutions of Compounds 1, 5, and 8, described in Table 1 above (Examples 1-3) were added to round-bottom flasks, and the solvents were removed using a rotary evaporator (as described by Nakamichi.) The flasks were rotated at 150 rpm, and the water bath was maintained at 50°C. The resulting solid material was stored under vacuum overnight at room temperature and then removed from the flask, pulverized, and size-selected via sieving to provide a 60 to 100 mesh powder.

Trial 1: Runs 1-3

The SDDs of Examples 1-3, and the rotary-evaporated material from Comparative Examples 1-3, were evaluated in an *in vitro* dissolution trial using the "centrifuge" method. This is the same test described in Example 3 of the pending Patent except that the dissolution solution was phosphate buffered saline (PBS) solution, as this solution is more similar to the JP2 solution used by Nakamichi. Samples were withdrawn and analyzed at different times. In this test, 2.88 mg of the SDD of Example 1 or the rotary evaporated dispersion (RED) of Comparative Example 1, 2.15 mg of the SDD of Example 2 or the RED of Comparative Example 2, or 2.70 mg of the SDD of Example 3 or the RED of Comparative Example 3, was added to a microcentrifuge tube. Each trial run was performed in duplicate. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL of phosphate buffered saline (PBS) at pH 6.5 and 290 mOsm/kg was added. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:6 (by volume) with methanol and then analyzed by high-performance liquid chromatography (HPLC). The contents of the tubes were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 5, 30, 60, 120, 180, and 1440 minutes. Crystalline Compound 1, Compound 5, and Compound 8 (0.36 mg, 0.36 mg, and 0.90 mg, respectively) were also tested for comparison. The concentrations of Compound obtained in these samples are shown in Table 2.

Table 2. Results of Trial 1

SDD = Spray Dried Dispersion

RED = Rotary Evaporated Dispersion

Run/Cmpd	Time (min)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 1 Run 1/Cmpd 1 SDD	0	0	
	5	37	
	30	58	
	60	70	
	120	80	
	180	93	12,900
	1440	120	
Trial 1 Run 1/Cmpd 1 RED	0	0	
	5	7	
	30	15	
	60	19	
	120	23	
	180	24	3500
	1440	28	
Trial 1 Run 1/Cmpd 1 Crystalline Cmpd (Control)	0	0	
	5	<2	
	30	<2	
	60	<2	
	120	<2	
	180	<2	<400
	1440	<2	
Trial 1 Run 2/Cmpd 5 SDD	0	0	
	5	196	
	30	189	
	60	192	
	120	139	
	180	110	28,400
	1440	48	

Run/Cmpd	Time (min)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 1 Run 2/Cmpd 5 RED	0	0	
	5	47	
	30	85	
	60	113	
	120	127	
	180	129	19,600
	1440	55	
Trial 1 Run 2/Cmpd 5 Crystalline Cmpd (Control)	0	0	
	5	5	
	30	5	
	60	7	
	120	7	
	180	6	1100
	1440	8	
Trial 1 Run 3/Cmpd 8 SDD	0	0	
	5	440	
	30	370	
	60	330	
	120	290	
	180	250	57,000
	1440	42	
Trial 1 Run 3/Cmpd 8 RED	0	0	
	5	350	
	30	380	
	60	340	
	120	320	
	180	260	58,100
	1440	14	

Run/Cmpd	Time (min)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 1 Run 3/Cmpd 8 Crystalline Cmpd (Control)	0	0	
	5	<5	
	30	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

The results of this test are summarized in Table 3, which shows the maximum concentration of SDD compounds in solution during the first 180 minutes of the test ($Cmax_{180}$), the area under the aqueous concentration versus time curve after 180 minutes (AUC_{180}), and the concentration at 1440 minutes (C_{1440}). Microcentrifuge dissolution test results for SDDs described in Examples 1-3, as well as REDs described in Comparative Examples 1-3, are all shown in Table 3 for comparison.

Table 3. Summary of Table 2

Example	Cmpd No.	Cmpd Conc. in the Dispersion (wt%)	Dosage (μgA/mL)	$Cmax_{180}$ (μgA/mL)	AUC_{180} (min*μg/mL)	C_{1440} (μgA/mL)
Ex 1	1	12.5	200	93	12,900	120
C1	1	12.5	200	24	3500	28
Crystalline cmpd	1	--	200	<2	<400	<2
Ex 2	5	16.7	200	196	28,400	48
C2	5	16.7	200	129	19,600	55
Crystalline cmpd	5	--	200	7	1100	8
Ex 3	8	33.3	500	440	57,000	42
C3	8	33.3	500	380	58,100	14
Crystalline cmpd	8	--	500	<5	<500	<5

These results show that dispersions formed by spray-drying resulted in increased Compound concentrations.over that of dispersions formed using rotary evaporation.

Trial 2: Runs 4-6

The SDDs of Examples 1-3, and the REDs from Comparative Examples 1-3, were evaluated in the saturation dissolution test described in US Patent 5,456,923 (Nakamichi). In this test, the SDDs and REDs were dosed into JP test solution 2 (0.2 M KH_2PO_4, adjusted to pH 6.8 using NaOH) at 25°C in a shaker bath for 24 hr at 24 cycles/min. Unlike Nakamichi (who sampled only after 24 hours), Applicants sampled the solutions at times that were physiologically relevant since absorption of Compound occurs primarily during the first several (i.e., 1 to 4) hours following ingestion. Samples were taken at 0, 60, 120, 180, and 1440 minutes. The samples were centrifuged at 40,000 rpm for 1 hr. This level of centrifugation may remove polymer and polymer/Compound aggregates from solution leading to an erroneously low estimate of bioavailability. The supernatant was analyzed by HPLC. Crystalline Compound 1, Compound 5, and Compound 8 were also tested for comparison. The concentrations of Compound obtained in these samples are shown in Table 4.

Table 4. Results of Trial 2

SDD = Spray Dried Dispersion

RED = Rotary Evaporated Dispersion

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 2 Run 4/Cmpd 1 SDD	0	0	
	60	23	
	120	23	
	180	23	3400
	1440	22	
Trial 2 Run 4/Cmpd 1 RED	0	0	
	60	6	
	120	10	
	180	13	1400
	1440	20	

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 2 Run 4/Cmpd 1 Crystalline Cmpd (Control)	0	0	
	60	<2	
	120	<2	
	180	<2	<400
	1440	<2	
Trial 2 Run 5/Cmpd 5 SDD	0	0	0
	60	191	
	120	160	
	180	138	25,200
	1440	28	
Trial 2 Run 5/Cmpd 5 RED	0	0	
	60	35	
	120	83	
	180	113	10,500
	1440	5	
Trial 2 Run 5/Cmpd 5 Crystalline Cmpd (Control)	0	0	
	60	5	
	120	5	
	180	5	800
	1440	5	
Trial 3 Run 6/Cmpd 8 SDD	0	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	
Trial 2 Run 6/Cmpd 8 RED	0	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 2 Run 6/Cmpd 8 Crystalline Cmpd (Control)	0	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

The results of this test are summarized in Table 5, which shows the maximum concentration of Compound in solution during the first 180 minutes of the test ($Cmax_{180}$), the area under the aqueous concentration versus time curve after 180 minutes (AUC_{180}), and the concentration at 1440 minutes (C_{1440}). Saturation dissolution test results for dispersions described in Examples 1-3 , as well as Comparative Examples 1-3, are shown in Table 5 for comparison.

Table 5. Summary of Table 4

Example	Cmpd No.	Cmpd Conc. in the Dispersion (wt%)	Dosage (μgA/mL)	$Cmax_{180}$ (μgA/mL)	AUC_{180} (min*μg/mL)	C_{1440} (μgA/mL)
Ex 1	1	12.5	200	23	3400	22
C1	1	12.5	200	13	1400	20
Crystalline cmpd	1	--	200	<2	<400	<2
Ex 2	5	16.7	200	191	25,200	28
C2	5	16.7	200	113	10,500	5
Crystalline cmpd	5	--	200	5	800	5
Ex 3	8	33.3	500	<5	<500	<5
C3	8	33.3	500	<5	<500	<5
Crystalline cmpd	8	--	500	<5	<500	<5

These results also show that dispersions formed by spray-drying resulted in equal or greater Compound concentration relative to that of materials formed using rotary evaporation. In some cases, particularly for Compound 8, Nakamichi's test method shows extremely low Compound levels at all times. However, other more physiologically relevant tests show much

higher Compound levels. Comparing results from Table 5 above to results in Table 2 of US Patent 5,456,923 shows that the rotary-evaporated material of Comparative Example 2 improves Compound 5 (nifedipine) concentration over that of crystalline Compound alone (as shown in US Patent 5,456,923); however, the spray-dried dispersion of Example 2 sharply improves Compound 5 concentration over that of the corresponding RED.

Trial 3: Runs 7-9

To demonstrate that the test differences between Nakamichi's and our test methods that are likely most relevant are the sample times and level of centrifugation, Applicants conducted the following dissolution test that used the method of Nakamichi (US Patent 5,456,923) except using: (1) shorter samples times and (2) less severe centrifugation. The SDDs of Examples 1-3, and the REDs from Comparative Examples 1-3, were evaluated in a saturation dissolution test similar to that described in US Patent 5,456,923. The saturation dissolution test was performed with the modification of less stringent centrifugation to allow polymer and the Compound in the form of polymer/Compound aggregates to remain in solution. In this test, the spray dried dispersions (SDDs) and rotary evaporated dispersions (REDs) were dosed into JP Test Solution 2 (0.2 M KH_2PO_4, adjusted to pH 6.8 using NaOH) at 25°C in a shaker bath for 24 hr at 24 cycles/min. Samples were taken at 0, 5, 30, 60, 120, 180, and 1440 minutes. The samples were centrifuged at 13,000 rpm for 1 minute. The supernatant was analyzed by HPLC. Crystalline Compound 1, Compound 5, and Compound 8 were also tested for comparison. The concentrations of Compound obtained in these samples are shown in Table 6.

Table 6. Results of Trial 2

SDD = Spray Dried Dispersion

RED = Rotary Evaporated Dispersion

Example	Time (hr)	Cmpd Concentration (µgA/mL)	AUC (min*µg/mL)
Trial 3/Run 7 Cmpd 1 SDD	0	0	
	5	26	
	30	28	
	60	29	

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
	120	29	
	180	30	5100
	1440	32	
Trial 3/Run 7 Cmpd 1 RED	0	0	
	5	3	
	30	4	
	60	8	
	120	11	
	180	14	1600
	1440	23	
Trial 3/Run 7 Cmpd 1 Crystalline Cmpd (Control)	0	0	
	5	<2	
	30	<2	
	60	<2	
	120	--	
	180	<2	<400
	1440	<2	
Trial 3/Run 8 Cmpd 5 SDD	0	0	
	5	140	
	30	199	
	60	220	
	120	220	
	180	176	35,600
	1440	41	
Trial 3/Run 8 Cmpd 5 RED	0	0	
	5	24	
	30	77	
	60	103	
	120	109	
	180	113	17,000
	1440	39	

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 3/Run 8 Cmpd 5 Crystalline Cmpd (Control)	0	0	
	5	2	
	30	2	
	60	2	
	120	3	
	180	4	500
	1440	5	
Trial 3/Run 9 Cmpd 8 SDD	0	0	
	5	270	
	30	300	
	60	280	
	120	290	
	180	240	49,300
	1440	133	
Trial 3/Run 9 Cmpd 8 RED	0	0	
	5	104	
	30	174	
	60	220	
	120	220	
	180	210	36,200
	1440	23	
Trial 3/Run 9 Cmpd 8 crystalline Cmpd (Control)	0	<5	
	5	<5	
	30	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

The results of this test are summarized in Table 7, which shows the maximum concentration of Compound in solution during the

first 180 minutes of the test ($Cmax_{180}$), the area under the aqueous concentration versus time curve after 180 minutes (AUC_{180}), and the concentration at 1440 minutes (C_{1440}). The modified saturation dissolution test results for dispersions described in Examples 1-3, as well as Comparative Examples 1-3, are all shown in Table 7 for comparison.

Table 7. Summary Of Table 6

Example	Cmpd No.	Cmpd Conc. in the Dispersion (wt%)	Dosage (μgA/mL)	$Cmax_{180}$ (μgA/mL)	AUC_{180} (min*μg/mL)	C_{1440} (μgA/mL)
Ex 1	1	12.5	200	30	5100	32
C1	1	12.5	200	14	1600	23
Crystalline cmpd	1	--	200	<2	<500	<2
Ex 2	5	16.7	200	220	35,600	41
C2	5	16.7	200	113	17,000	39
Crystalline cmpd	5	--	200	<14	500	5
Ex 3	8	33.3	500	300	49,300	133
C3	8	33.3	500	220	36,200	23
Crystalline cmpd	8	--	500	<5	<500	<5

The Compound concentrations observed for the saturation dissolution tests of Example 6 were greater than the concentrations observed in the tests of Example 5. This is due to less stringent centrifugation of samples for Example 6, which allowed the Compound to remain in solution. These results more clearly show that dispersions formed by spray-drying resulted in increased Compound concentration over that of dispersions formed using rotary evaporation.